

## The Origin of Plagues: A Research Agenda for the 21st Century

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**Abstract:** Viruses, bacteria, and parasites emerge in both new and old forms to cause epidemics. Old microbes can produce new epidemics because of changes in the life style (including increased international travel) of people and societies. But epidemics occur also as a consequence of new genetic variations in microbes. These various epidemics connect the future with the past, offering lessons for guarding the health of generations to come—lessons learned from diseases such as malaria, tuberculosis, influenza, and acquired immunodeficiency syndrome (AIDS). The public must be vigilant to the possibility of new epidemics. The research agenda for the 21st Century is to learn more about the biology and epidemiology of microbes, and strengthen the worldwide systems of surveillance and detection.

It is a great pleasure for me to be in Japan once again. Since 1975, I have had a close affiliation with my Japanese colleagues, particularly through the U. S.-Japan Cooperative Medical Sciences Program. This research program is concerned with diseases that occur in southeast Asia and elsewhere in this troubled world. I am a member of the U. S. Delegation to the Joint Committee which oversees this program in biomedical research. Through the years, I have had the pleasure of working with the late Professor Kurokawa when he was Chairman of the Japanese Delegation, with Professor Suwa, a former Chairman, and most recently, Professor Someya, the current Chairman. Through this program both Japanese and U. S. scientists have collaborated on parasitic and virus diseases, cholera, AIDS, and tuberculosis. In 1990 the 25th Anniversary of the U. S.-Japan Program was celebrated in Tokyo. In a message prepared for that occasion, Prime Minister Kaifu said: The achievements of this program “represent examples of the fruits of close cooperation between our two nations for the greater prosperity and well-being of the entire world.”

Acquired immunodeficiency syndrome (AIDS) is the most recent example of our susceptibility to the microbial world. Will a “new” microbe, or a genetic variation of an old one “go global” as AIDS has done? An unexpected epidemic may be incubating even now in the crowded, unsanitary mega-cities of the developing world, or in remote jungles in Africa, South America, or Asia—once sparsely inhabited regions that have recently been altered by modern civilization.

Indeed, strange epidemics have been occurring in far away places. In Africa, outbreaks of the deadly Ebola virus took the lives of 50% of the people who became infected. A majority of the doctors and nurses who treated these patients also died of the disease. After fatal but localized outbreaks of Ebola fever, the disease failed to become a worldwide epidemic.

But at the same time the AIDS virus was spreading silently throughout Central Africa, only to spill over to U. S. and Europe, and now Asia. It did go global.

Many factors interact and contribute to the reemergence of old infectious diseases or the emergence of new ones (Krause, 1992). More often than not, epidemics occur because of changes in the patterns of human behavior, social organization, urbanization, and agriculture. But the most important factor is the spread far and wide of microbial organisms from points of origin as a result of the migration and travel of people.

In ancient times, infectious diseases such as measles and smallpox spread slowly but steadily along caravan routes throughout the Roman and Asian world. After 1492, the oceans became highways that further extended the dispersal of disease agents. Plagues such as smallpox and measles circled the globe within a year. But today, air-borne travelers incubating infections can reach any point on the globe in 24 hours. As a consequence, worldwide exposure to a highly infectious virus, such as influenza, occurs in a matter of weeks.

However, microbes are not idle bystanders, waiting for new opportunities offered by human mobility, ignorance, or neglect. Microbes possess remarkable genetic versatility that enables them to develop new pathogenic vigor, to escape population immunity by acquiring new antigens, and to develop antibiotic resistance.

For all of these reasons the origins of plagues will dominate the research agenda for the 21st Century. It is necessary to be prepared for new epidemics caused by old microbes as well as those caused by new microbes as a consequence of genetic and evolutionary events. Examples of early and recent epidemics are described here to illustrate the principles that govern the occurrence of plagues.

### *Tuberculosis*

"Drug resistant TB may bring epidemics" is headlined in a recent issue of *Nature*, "...a scourge that industrialized nations thought had been eradicated..." Why does this "captain of these men of death" again stalk the globe? It is useful in the context of old microbes that reemerge, as TB has done, to recount here the prior epidemic of tuberculosis in the 18th and 19th centuries.

The whole tragic story of tuberculosis has been told by Rene and Jean Dubos in *The White Plague: Tuberculosis, Man and Society*. "...As the number of deaths mounted throughout the first half of the century, it became obvious that the gravity of the disease could no longer be concealed... Tuberculosis was the Great White Plague threatening the very survival of the European race... Miserable humanity was living in the dreary tenements born of the industrial revolution... Men, Women, and pale children... cold and starving worked long hours in dark and crowded shops. Tuberculosis was there breeding suffering and misery..." (Dubos and Dubos, 1952). The slums of the big industrial cities became cauldrons for the incubation of tuberculosis, and when they boiled over, the disease spread to the upper classes and rural communities.

Now tuberculosis, armored with antibiotic resistance, is again advancing into new

undercurrents of opportunity, the poverty-stricken populations of the inner cities of the United States and the malnourished in developing countries. Indeed, in the last year patients have died within months with rapidly progressive consumption due to bacteria resistant to *all* anti-tuberculosis drugs. The AIDS epidemic also opens up an expanding population that is especially susceptible to TB. What will happen when AIDS and TB gallop together throughout Africa, Asia, and elsewhere? (Bloom and Murrag, 1992).

Microbes including tuberculosis have a generous supply of genetic mechanisms by which they acquire antibiotic resistance; for example, chromosomal mutation, or inductive expression of a latent chromosomal gene. Mechanisms of genetic exchange between bacterial clones include transformation, transduction, or conjugation by plasmids. In addition, bacteria may possess transposons, the so-called jumping genes, that have the ability to enter transmissible plasmids or chromosomes. Resistance can be transferred horizontally by plasmids, or by chromosomally located conjugative transposons that spread the resistance to other species.

Despite the progress in the control of TB in Europe, Japan and the United States, tuberculosis we should remember has remained a leading cause of death in developing countries. And now these people must contend with a new challenge: a genetically versatile microbe resistant to antibiotics and swept along on the tide of AIDS, poverty and malnutrition. A challenge indeed for the 21st Century. Just two weeks ago in Bethesda, the World Congress on Tuberculosis developed a research and public health agenda to conquer tuberculosis. But time is running out. "Where there is no vision, the people perish." (Bloom and Murray, 1992)

### THE CHALLENGE OF MALARIA

*Plasmodium falciparum*, like the human immunodeficiency virus, is a major disease in the tropical world that will become worse in the years ahead with no guaranteed solution at hand. "The malaria epidemic is out of control," Louis Miller has told us. What is more striking than the reemergence of malaria in Sri Lanka? The disease had been eliminated. But now, as in so many parts of the world, it is epidemic. I need not remind this audience that the resurgence of malaria is a consequence of chloroquine resistant malaria and DDT resistant mosquitoes. Such resistance stems from the plasticity of both species to survive through genetic change and adaptation; a plasticity that is shared with all living things that swim in the evolutionary stream.

Miller (1992) has outlined a long range strategy to develop new methods of treatment and prevention. *First*, we must remain committed to the search for a malaria vaccine.

*Second*, we must renew the attack on the mosquito vector. "To appreciate the potential of this approach, it is only necessary to remember the dramatic effect that DDT had on reducing or eliminating malaria from many parts of the world. It is for this reason that we look with hope to research efforts to alter the capacity of mosquitoes to transmit malaria." Would it be possible, for example, to block the development of the malaria parasite in the mosquito. This might be done by introducing genes into the vectors that block development.

*Finally*, we must examine the biochemical pathways unique to the malaria parasite, and develop drugs based on such new biochemical knowledge. One such area of promise is hemoglobin digestion. "The parasite, after digestion of hemoglobin, reorganizes heme into a nontoxic compound, hemozoin pigment. The polymeric structure of hemozoin pigment has recently been identified, and the polymerizing enzyme activity is blocked by chloroquine and other related antimalarial compounds. Furthermore, the locus of the chloroquine resistance gene, which encodes a drug-efflux mechanism should open the way for drug design to reverse chloroquine resistance." This and other strategies must be pursued with renewed vigor.

Malaria has been called the King of Diseases. And so it remains. Will we topple his throne and defeat the King in the 21st Century?

#### INFLUENZA; AN OLD VIRUS IN GARMENTS

We live in the shadow of the frightful 1918 pandemic of influenza. More people died from influenza than were killed in four years of massacre during World War I. Most virologists predict history will repeat itself. It is just a matter of time. Will we be ready?

"New" and novel influenza viruses such as the one that caused the 1918 pandemic arise from genetic reassortment. Such reassortment results in a major evolutionary leap and the occurrence of an entirely new hemagglutinin antigen against which there is little or no immunity. A pandemic of influenza is the result. This occurred in 1957 (Asian flu) and in 1968 to 1969 (Hong Kong flu). The new influenza hemagglutinin in 1957 is designated H2 and that in 1968 is designated H3. Both viruses possess neuraminidase N2. The viruses causing these epidemics are thought to have arisen through the capture by human viruses of one or more external genes from avian influenza viruses at the time of co-infection of the two viruses in the same animal or human. Such events most likely occurred in China or elsewhere in Asia and resulted in new viruses (Kilbourne, 1990).

The generation of these new viruses occurs as a consequence of co-infection because the influenza viruses carry their genetic material in eight separate gene segments. During the course of co-infection with different strains, these genes can be reassorted or recombined, producing novel viruses that possess gene combinations unlike those of either parent. As Kilbourne notes, "The process is analogous to sexual reproduction. Influenza viruses can make evolutionary leaps without the need to gradually accumulate numerous favorable mutations."

Point mutations that alter critical sites on the major hemagglutinin glycoprotein antigen of influenza virus allow the virus to elude population immunity that occurs following a pandemic. Such changes in the virus account for the antigenic drift in the hemagglutinin of wild-type viruses that occur from year to year. Because the new hemagglutinin bears some resemblance to the old, antibodies to the old hemagglutinin may, but do not always, neutralize the "new" virus. Therefore, the "new" virus may cause infection even in those who had influenza in previous years.

For these reasons influenza is a moving target, and worldwide surveillance is needed to determine the emergence of new strains and their use in formulating an up-to-date flu vaccine. Indeed we have been reasonably successful through this worldwide effort in diminishing the attack rates of influenza with immunization. And yet when will genetic reassortment give birth to a brand new virus as vicious as its predecessors? We must be ready in the 21st Century.

#### AN AGENDA FOR THE 21ST CENTURY

In 1962, Sir MacFarlane Burnet wrote that infectious diseases were almost "something that has passed into history", and "they would be virtually eliminated as a significant factor in our social life at the dawn of the next century". Burnet was not alone in these predictions. The medical and scientific community and the general public by and large accepted this verdict, and the major research effort in the 1970s turned to the great "killers and crippers," heart disease and cancer. And yet there is every reason to believe that epidemics will occur in the future just as they have in the past.

First, history is a record of changes in the behavior and customs of humans and society—in manufacturing, farming, animal husbandry, migration, urbanization, war, love, and courtship. Furthermore, changes in these matters will provide opportunities that can be exploited by microbes to produce unexpected epidemics in the decades to come; just as such changes in the past have fomented earlier epidemics and now AIDS. Second, there is no way that science can halt the future occurrence of "new" microbes. These emerge from the evolutionary stream as a consequence of genetic events and selective pressures that favor the "new" over the "old". It is nature's way.

So we need an agenda for the 21st Century if we are to compete successfully with the restless tide of microbes (Krause, 1981; Lederberg *et al.*, 1992). Our surveillance system must be strengthened and, most especially, surveillance efforts must be expanded in other regions of the world. Global diseases require global surveillance.

But surveillance alone is not enough. We must expand the circle of knowledge through research on the epidemiology and biology of microbes. Research must push ahead into still-unknown areas concerning the lives of microbes—how they live, survive, and adapt to new habitats. We must understand fully the genetic make-up of microbes and their talent to cause disease. We must better understand the immunological processes that are mobilized by the body in defense against microbial invasion and infection.

Finally, we must be aware of the possible consequences when we alter our human and social behavior and medical practices. What new undercurrent of opportunity will be created for microbes as our cities become larger and more crowded, when perhaps 50 million people will be crowded together in one sprawling, cluttered urban area? What unexpected plagues will spill over from these cauldrons as tuberculosis did in the slums and sweatshops of the Victorian Age? Will global warming enhance the overgrowth of microbes in the evolutionary stream? Will tropical diseases find a congenial habitat in previously temperate latitudes?

What new highways will microbes travel as humans change the world's topography, converting tropical forests and other habitats into cities and farms? All of these changes foreshadow the origin of plagues in the years to come; a research agenda for the 21st Century.

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